Chemistry of 6*H*-Pyrido[4,3-*b*]carbazoles. Part V.[1] A Simple Synthesis of Ellipticines

By **Malcolm Sainsbury** * and **Raymond F. Schinazi**, School of Chemistry, University of Bath, Claverton Down, Bath BA2 7AY

A new versatile synthesis of 6*H*-pyrido[4,3-*b*]carbazoles (ellipticines) is described which requires mild conditions and utilises easily accessible starting materials [indoles and 3-(1-chloroalkyl)pyridines]. It is illustrated by the synthesis of 11-demethylellipticine, ellipticine, and 8,9-methylenedioxyellipticine. Overall yields compare favourably with those of previous syntheses.

SINCE certain 6*H*-pyrido[4,3-*b*]carbazoles (ellipticines) show promise as potential anticancer drugs,[2] numerous synthetic routes to them have been devised.[1a,3] There are, however, problems inherent in all preparations so far described, and our intention has been to develop an efficient synthesis of wide application requiring both readily available starting materials and the mildest reaction conditions. In view of this we have always been attracted by the simplicity of Woodward's original three-step sequence to ellipticine (2; R = Me)[4a] (Scheme 1). Unfortunately this route has no practical

[1] (*a*) Part IV, M. Sainsbury, B. Webb, and R. F. Schinazi, *J.C.S. Perkin I*, 1975, 289; (*b*) preliminary report M. Sainsbury and R. F. Schinazi, *J.C.S. Chem. Comm.*, 1975, 540.

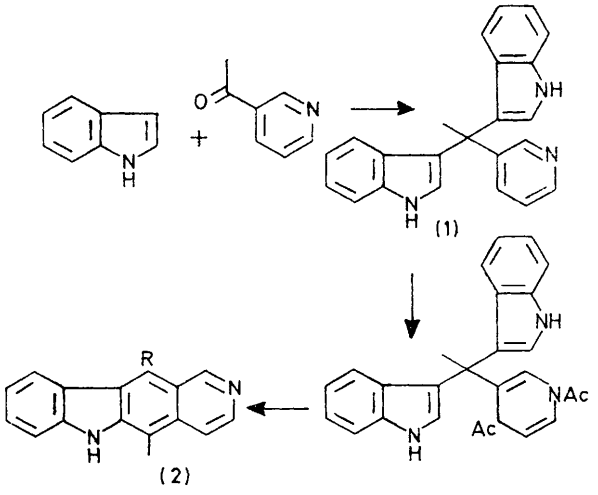
[2] M. Hayat, G. Mathé, M. M. Janot, P. Potier, N. Dat-Xuong, A. Cavé, T. Sévenet, C. Kan-Fan, J. Poisson, J. Miet, J. Le Men, F. Le Goffic, A. Gouyette, A. Ahond, L. K. Dalton, and T. A. Connors, *Biomedicine*, 1974, **21**, 101, and references cited therein.

[3] (*a*) P. A. Cranwell and J. E. Saxton, *J. Chem. Soc.*, 1962, 3842; (*b*) T. R. Govindachari, S. Rajappa, and V. Sundarsanam, *Indian J. Chem.*, 1963, **1**, 247; (*c*) L. K. Dalton, S. Demerac, B. C. Elmes, J. W. Loder, J. M. Swan, and T. Teitei, *Austral. J. Chem.*, 1967, **20**, 2715; (*d*) F Le Goffic, A. Gouyette, and A. Ahond, *Compt. rend.*, 1972, **274C**, 2008; (*e*) T. Kametani, Y. Ichikawa, T. Suzuki, and F. Fukumoto, *Tetrahedron*, 1974, **30**, 3713; (*f*) R. Besselievre, C. Thal, H. P. Husson, and P. Potier, *J.C.S. Chem. Comm.*, 1975, 90; (*g*) K. N. Kilminster and M. Sainsbury, *J.C.S. Perkin I*, 1972, 2264; (*h*) M. Sainsbury and B. Webb, *ibid.*, 1974, 1560; (*i*) R. W. Guthrie, A. Brossi, F. A. Mennona, J. G. Mullin, and R. W. Kierstead, *J. Medicin. Chem.*, 1975, **18**, 755; (*j*) Y. Langlois, N. Langlois, and P. Potier, *Tetrahedron Letters*, 1975, 955.

[4] (*a*) R. B. Woodward, G. A. Iacobucci, and F. A. Hochstein, *J. Amer. Chem. Soc.*, 1959, **81**, 4434; (*b*) J. Bergman and R. Carlsson, *J. Heterocyclic Chem.*, 1972, **9**, 833.

value since the overall yield is extremely low and the conditions in the final step are severe. These disadvantages arise because the second stage operates through a complex dimerisation–disproportionation mechanism [5] for which the bulky intermediate (1) is a poor substrate and, in the final oxidative cyclisation reaction, the ' extra ' indolyl unit is only removed with difficulty, under pyrolytic conditions.

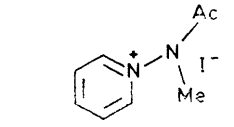
We considered that if the conditions for the initial condensation between the indole and pyridine units could be moderated to afford a ' 1 : 1 ' product, then these constraints would be partly removed although, necessarily, the second stage (reductive acetylation) is limited to a maximum yield of 50%.[5] (In practice, even with simple pyridines, the yield is more usually 10—20%.[3g,h]) Suzue *et al.*,[6] however, have reported that pyridine can be converted into the *N*-amidopyridinium salt (3), which with potassium cyanide gives 4-cyanopyridine. This reaction has wide application



SCHEME 1

and from the product nitriles the corresponding acetyl derivatives are readily prepared by the action of methyllithium, followed by hydrolysis of the intermediate imine.[1a] Since the yields in this procedure are almost quantitative, we considered that the second obstacle to the Woodward approach was overcome, leaving only the problems of the condensation reaction to be solved.

Although acidic conditions favour a product containing two indolyl units,[4g,h] Potier has shown [7] that at room temperature the aldehyde (4) combines with indole in the presence of aqueous base to give the alcohol (5; R^1 = OH, R^2 = H); this on hydrogenolysis affords the 3-methylindole derivative (5; $R^1 = R^2$ = H). Unfortunately, 3-acetylpyridine is much less reactive than the aldehyde (4) towards indole: under Potier's conditions it does not react, and even with 5,6-methylenedioxyindole the reaction is very slow. Thus only a 2% yield of the alcohol (6) was obtained after 1 month. All attempts to accelerate these processes result in complex products.



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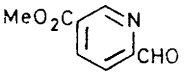

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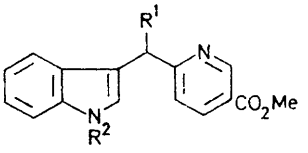

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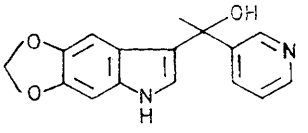
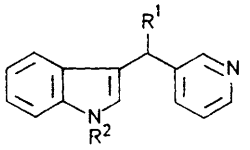


(6)

It is known that 3-(halogenomethyl)pyridines and indolylmagnesium bromide give the corresponding 3-(pyridylmethyl)indole (7; $R^1 = R^2$ = H),[8] but at first we were prevented from repeating this reaction with the bromo-compound (8; X = Br) because treatment of the alcohol (8; X = OH) with phosphorus tribromide gave only polymeric products. However, when the alcohol was treated with toluene-*p*-sulphonyl chloride in the presence of sodium acetate, the acetate ester (8; X = OAc) was formed and, similarly, with methanesulphonyl chloride the chloro-compound (8; X = Cl) was obtained. (This last compound is stable at 0—10 °C.) Accordingly, a mixture of alcohol and indole in dry benzene was treated with methanesulphonyl chloride in the expect-



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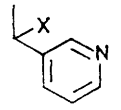

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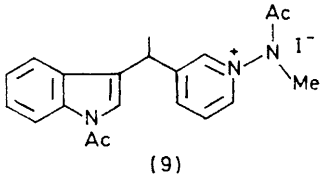

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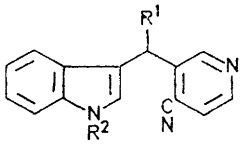

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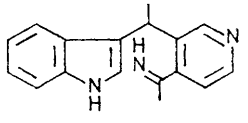

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ation of forming compound (7; R^1 = Me, R^2 = H), and on work-up, a 30% yield of the required 3-ethylindole

[5] J. W. Wibaut and J. F. Arens, *Rec. Trav. chim.*, 1941, **60**, 119; P. M. Atlani and J. F. Bielmann, *Tetrahedron Letters*, 1969, 4829; P. M. Atlani, J. F. Bielmann, R. Briere, H. Lemaire, and A. Rassat, *Tetrahedron*, 1972, 2827.

[6] S. Suzue, M. Hirobe, and T. Okamoto, *Yakugaku Zasshi*, 1973, **93**, 1331.

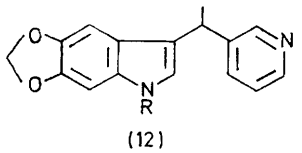
[7] Y. Langlois and P. Potier, *Tetrahedron*, 1975, **31**, 419.

[8] J. I. DeGraw, J. G. Kennedy, and W. A. Skinner, *J. Heterocyclic Chem.*, 1966, **3**, 67.

was obtained. The same product was also produced, in better yield (49.5%), by the action of indolylmagnesium bromide on the chloro-compound (8; X = Cl), prepared either as above or by treating the alcohol (8; X = OH) with thionyl chloride.

With the 3-ethylindole (7; R^1 = Me, R^2 = H) to hand, the remaining steps to ellipticine were easily accomplished in 25—30% overall yield. Thus the salt (9), prepared from the *N*-acetyl derivative (7; R^1 = Me, R^2 = Ac) by the action in turn of *O*-mesitylsulphonylhydroxylamine, acetic anhydride, and methyl iodide,[9] was treated with potassium cyanide and ammonium chloride to give the nitrile (10; R^1 = Me, R^2 = Ac). This was deacetylated by elution through a short column of basic alumina with chloroform as solvent; the product reacted with methyl-lithium and the intermediate imine (11) was hydrolysed and cyclised directly to ellipticine by warming in aqueous 20% acetic acid.

By the same procedures 11-demethylellipticine (2; R = H) was obtained from the 3-methylindole derivative (7; R^1 = R^2 = H) * (yield 28%), and 8,9-methylenedioxyellipticine (14) from (12; R = H) *via* the cyano-derivative (13) (overall yield 65%).



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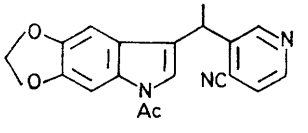

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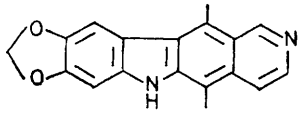

(14)

EXPERIMENTAL

U.v. spectra were recorded for solutions in 95% aqueous ethanol; i.r. data refer to Nujol mulls; ^{1}H n.m.r. spectra were recorded at 60 or 100 MHz for solutions in deuteriochloroform unless stated otherwise, with tetramethylsilane as an internal standard.

Condensation Attempts between 3-Acetylpyridine and Indoles.—(*a*) Indole (1.16 g) and 3-acetylpyridine (1.21 g) in glacial acetic acid were heated under reflux for 2 h. After cooling, the mixture was poured into aqueous sodium hydroxide (7%; 8 cm^3). The solid formed was recrystallised from ethanol to give white prisms of 1,1-di-indol-3-yl-1-(3-pyridyl)ethane (1) (1.1 g, 33%), m.p. 251—252° (from ethanol) [lit.,[4b] 253° (decomp.)]; *m/e* 337 (M^+) and 322 (base).

(*b*) 5,6-Methylenedioxyindole [10] (1.61 g) in methanol (7.5 cm^3) and 10M-sodium hydroxide (0.14 cm^3) was cooled to 0 °C. To the stirred solution 3-acetylpyridine (1.21 g) was added dropwise at 0 °C, and the mixture was then stirred overnight at 0 °C. T.l.c. showed the presence of three components. The mixture was stored for 1 month at room temperature, during which time some crystals were formed. These were filtered off and washed with cold methanol to yield white prisms of 1-(5,6-*methylenedioxyindol*-3-*yl*)-1-(3-*pyridyl*)*ethanol* (6) (50 mg, 2%), m.p. 185—186° (from methanol), *m/e* 282 (M^+), 264 (base), 253, 239, and 255; $\nu_{max.}$ 3 540, 3 100, and 1 300 cm^{-1}; δ [$CDCl_3$–5% $(CD_3)_2SO$] 10.15br (1 H, s, NH), 8.7 (1 H, d, *J* 2 Hz, pyridyl 2-H), 8.4 (1 H, d, *J* 5 Hz, pyridyl 6-H), 7.8 (1 H, dd, *J* 5 and 2 Hz, pyridyl 4-H), 7.25 (2 H, m, indole 2- and pyridyl 5-H), 6.85 (1 H, s, indole 7-H), 6.8 (1 H, s, indole 4-H), 5.85 (2 H, s, O·CH_2·O), 5.13br (1 H, s, OH), and 1.94 (3 H, s, CH_3) (Found: C, 67.9; H, 5.1; N, 9.8. $C_{16}H_{14}N_2O_2$ requires C, 68.1; H, 5.0; N, 9.9%).

Nicotinoyl Chloride (*Optimised Procedure*).—Nicotinic acid (48 g) was heated at reflux for 30 min with thionyl chloride (150 cm^3) under anhydrous conditions. The excess of thionyl chloride was then removed by evaporation *in vacuo* and by azeotropic distillation with dry benzene. The white needles of nicotinoyl chloride hydrochloride were covered with ether and the mixture was stirred with dry triethylamine (40 g) overnight. The triethylamine hydrochloride formed was filtered off and the solution of nicotinoyl chloride in ether was stored under anhydrous conditions.

Indol-3-yl 3-Pyridyl Ketone.—The ethereal solution of nicotinoyl chloride was placed in an ice–salt bath, and a solution of indol-3-ylmagnesium bromide (1 mol equiv.) was added dropwise, with the temperature maintained between −5 and 0 °C. The mixture was stirred for a further 2 h at 0 °C and then left overnight at room temperature. The organometallic complex was hydrolysed with a saturated solution of ammonium chloride and the mixture was extracted several times with dichloromethane. The red organic phase was dried ($MgSO_4$) and evaporated *in vacuo* to yield a thick gum. This was dissolved in propan-2-ol (200 cm^3) and cooled to furnish *3-indolyl 3-pyridyl ketone* (21.4 g, 25%) as white cubes, m.p. 210—211°; $\lambda_{max.}$ 260sh (ε 14 350), 269 (14 750), and 322 nm (13 800); $\nu_{max.}$ 1 597 (C=O) and 3 175 cm^{-1} (N–H); δ [$(CD_3)_2SO$] 12.20br (1 H, s, NH), 9.05 (1 H, d, *J* 1.5 Hz, pyridyl 2-H), 8.80 (1 H, d, *J* 1.5 Hz, pyridyl 6-H), 8.0—8.50 (3 H, m, pyridyl 4- and 5- and indolyl 4-H), 7.2—7.70 (4 H, m, indolyl 2-, 5-, 6-, and 7-H), *m/e* 222 (M^+) and 144 (base) (Found: C, 75.5; H, 4.55; N, 12.45. $C_{14}H_{10}N_2O$ requires C, 75.65; H, 4.55; N, 12.45%).

N-Acetylindol-3-yl 3-Pyridyl Ketone.—3-Indolyl 3-pyridyl ketone (1.5 g) was heated under reflux for 1 h with acetic anhydride (30 cm^3). The solvent was removed by evaporation *in vacuo* and the residue crystallised from ethanol to furnish the title compound as pale yellow *needles* (86%), m.p. 173—175°; $\lambda_{max.}$ 210 (ε 19 600), 228 (26 500), 252 (14 400), and 309 nm (11 100); $\nu_{max.}$ 1 730 (NAc) and 1 630 cm^{-1} (vinylogous amide C=O); δ 9.04 (1 H, s, pyridyl 2-H), 8.78br (1 H, d, *J* 4.5 Hz, pyridyl 6-H), 8.0—8.47 (3 H, complex, pyridyl 4- and 5- and indolyl 4-H), 7.84 (1 H, s, indolyl 2-H), 7.24—7.51 (3 H, complex, indolyl 5-, 6-, and 7-H), and 2.62 (3 H, s, NAc) (Found: C, 72.5; H, 4.5; N, 10.7. $C_{16}H_{12}N_2O_2$ requires C, 72.7; H, 4.6; N, 10.6%).

Reduction of 3-Indolyl 3-Pyridyl Ketone with Sodium Borohydride.—(a) *Reduction at* 25 °C. The ketone (10 g) was dissolved in warm aqueous ethanol (300 cm^3) and

* Prepared by the action of nicotinoyl chloride on indolylmagnesium bromide and reduction of the product with sodium borohydride.

[9] Y. Tamura, J. Minamikawa, Y. Miki, S. Matsugashita, and M. Ikeda, *Tetrahedron Letters*, 1972, **40**, 4133.

[10] F. Dallacker and D. Bernabei, *Monatsh. Chem.*, 1967, **98**, 785.

sodium borohydride was added in portions with stirring, with the temperature maintained at 25—30 °C. Addition of borohydride was stopped when the u.v. spectrum of the solution showed no further change. The excess of reagent was then decomposed by careful addition of acetone. The mixture was evaporated to dryness *in vacuo* at 45—50 °C and the residue partitioned between water (100 cm³) and chloroform (100 cm³). The organic phase was dried ($MgSO_4$) and evaporated to low bulk; *indol-3-yl-(3-pyridyl)-methanol* crystallised as needles (9.3 g, 92%), m.p. 154—155°, $\lambda_{max.}$ 268 (ε 8 000), 280sh (7 200), and 288 nm (6 140); $\nu_{max.}$ 3 270 (O–H), 3 140 (N–H), and 1 240 cm⁻¹ (C–O); δ [$(CD_3)_2SO$] 10.55br (1 H, s, NH), 8.70br (1 H, s, pyridyl 2-H), 8.40br (1 H, d, *J* 5 Hz, pyridyl 6-H), 6.85—7.95 (7 H, m, remaining aromatic protons), 6.10 (1 H, d, *J* 4 Hz, C*H*·OH), 5.65 (1 H, d, *J* 4 Hz, OH) (on treatment with deuterium oxide the peak at δ 5.65 disappears and the signal at 6.10 collapses to a sharp singlet); *m/e* 224 (M^+) and 206 (base) (Found: C, 75.3; H, 5.4; N, 12.4. $C_{14}H_{12}N_2O$ requires C, 75.0; H, 5.4; N, 12.5%).

(b) *Reduction in boiling aqueous ethanol.* The ketone (1.5 g) was dissolved in 95% ethanol (50 cm³) and an excess of sodium borohydride was added in portions to the boiling solution. After 30 min the solvent was removed *in vacuo* and the residue extracted with water and chloroform. The chloroform extract was washed, dried ($MgSO_4$), and evaporated to dryness. Trituration of the yellow gum with ether furnished a pale yellow amorphous solid (7; $R^1 = R^2 = H$) (1.0 g, 72%), which crystallised from acetone–ether as almost colourless cubes, m.p. 157—158° (lit.,[8] 154—156°), $\lambda_{max.}$ 270 (ε 8 500), 282 (7 400), and 291 nm (6 400); $\nu_{max.}$ 3 110 cm⁻¹ (NH); δ 10.40br (1 H, s, NH), 8.50br (1 H, s, pyridyl 2-H), 8.35 (1 H, d, *J* 5 Hz, pyridyl 6-H), 6.9—7.6 (7 H, complex, remaining aromatic protons), and 4.05 (2 H, s, ArCH_2Ar); *m/e* 208 (M^+) and 92 (base) (Found: C, 80.3; H, 5.6; N, 13.5. Calc. for $C_{14}H_{12}N_2$: C, 80.7; H, 5.8; N, 13.5%).

1-(3-*Pyridyl*)*ethyl Acetate* (8; X = OAc).—1-(3-Pyridyl)-ethanol (2 g) and toluene-*p*-sulphonyl chloride (5 g) were dissolved in benzene (60 cm³) and solid anhydrous sodium acetate (1.3 g) was added. The mixture was heated and stirred on a steam-bath for 2 h, and then left at room temperature overnight. Water (50 cm³) was added and the two phases were separated. The aqueous phase was basified with ammonia solution (*d* 0.89) and extracted with chloroform. The extracts were washed with brine, dried ($MgSO_4$), and evaporated *in vacuo* to yield the *acetate* as a yellow oil (0.5 g), b.p. 62° at 0.08 mmHg, $\nu_{max.}$ 1 730 and 1 235 cm⁻¹; $\lambda_{max.}$ 256, 262, and 270 nm; δ 8.7—5 (2 H, m, pyridyl 2- and 6-H), 7.8—7.55 (1 H, m, pyridyl 4-H), 7.35—7.10 (1 H, m, pyridyl 5-H), 5.9 (1 H, q, *J* 6.5 Hz, C*H*·CH_3), 2.05 (3 H, s, OAc), and 1.55 (3 H, d, *J* 6.5 Hz, CH·CH_3) (Found: C, 65.35; H, 6.6. $C_9H_{11}NO_2$ requires C, 65.45; H, 6.7%). The same product was obtained from the alcohol by the action of acetyl chloride.

3-(1-*Chloroethyl*)*pyridine* (8; X = Cl).—The alcohol (8; X = OH) (2 g) in benzene was heated on a water-bath with methanesulphonyl chloride (1 cm³) for 30 min. After cooling, water (50 cm³) was added and the aqueous phase separated, basified, and worked up to give the title compound (0.8 g) as a mobile, unstable liquid, $\nu_{max.}$ 650 cm⁻¹. This compound has been prepared previously in this laboratory by the action of thionyl chloride on the alcohol (8; X = OH) and characterised by conversion into 3-(1-methoxyethyl)pyridine with sodium methoxide.[3g]

3-[1-(3-*Pyridyl*)*ethyl*]*indole* * (7; R^1 = Me, R^2 = H).—(*a*) Methanesulphonyl chloride (1 cm³) in dry benzene was added slowly (4 h) to a mixture of indole (1.2 g) and the alcohol (8; X = OH) (1.2 g) in the same solvent under reflux in a Dean–Stark apparatus. At the end of the reaction the benzene was decanted from oil which had separated and the latter was then dissolved in water and washed several times with ether. The aqueous phase was basified with ammonia and extracted with chloroform; the combined chloroform extracts were dried and evaporated to give an orange-coloured oil. On trituration with benzene this gave the title compound as a colourless *solid* (0.7 g, 30%), m.p. 173—174°; *m/e* 222 (M^+), 207 (base), and 144; $\nu_{max.}$ 3 140, 1 590, 1 580, and 1 030 cm⁻¹; δ 8.7br (1 H, s, NH), 8.64 (1 H, d, *J* 2 Hz, pyridyl 2-H), 8.42 (1 H, dd, *J* 6 and 2 Hz, pyridyl 6-H), 7.6—6.9 (7 H, m, indole 2-, 4-, 5-, 6-, and 7- and pyridyl 4- and 5-H), 4.4 (1 H, q, *J* 10 Hz, C*H*·CH_3), and 1.7 (3 H, d, *J* 10 Hz, CH·CH_3) (Found: C, 81.0; H, 6.4; N, 12.4. $C_{15}H_{14}N_2$ requires C, 81.1; H, 6.4; N, 12.6%).

(*b*) An ethereal solution of ethylmagnesium bromide [from ethyl bromide (10.8 cm³)] was placed in an ice–salt bath, and indole (16.56 g, 0.142 mol) in dry ether (35 cm³) was added dropwise. After 30 min the indolylmagnesium bromide had settled as a dense grey suspension, leaving a colourless ether layer above. The suspension was allowed to warm to room temperature and then stirred for 1 h. The solution was then cooled to 0 to −5 °C and 3-(1-chloroethyl)pyridine (8; X = Cl) (8.86 g, 0.07 mol) was added rapidly. The solution was stirred for 1 h at 0 °C and then allowed to warm slowly to room temperature. The resulting mixture was stirred for 48 h at room temperature and then cooled to 0 °C. Hydrochloric acid (2M; 50 cm³) was added and the mixture was shaken until most of the gum had dissolved. The layers were separated, and the aqueous layer washed with ether (50 cm³), adjusted to pH 9—10 with concentrated ammonia, and extracted with chloroform (2 × 100 cm³). The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo* to leave an oil. On trituration with ether the oil afforded the title compound as a white solid which was filtered off and recrystallised from ethanol to yield prisms (7.7 g, 49.5%).

When a mixture of ethylmagnesium bromide, indole, and the chloropyridine (molar ratios 1 : 1 : 1) was used, a 22.4% yield of (7; R^1 = Me, R^2 = H) was obtained. Addition of benzene, tetrahydrofuran, or dichloromethane to solubilise the intermediate complex did not increase the yield of product. Heating the mixture of indolylmagnesium bromide and the chloropyridine (8; X = Cl) with or without the above-mentioned solvents, at any stage during the reaction, reduced the yield of final product.

1-*Acetyl*-3-[1-(3-*pyridyl*)*ethyl*]*indole* (7; R^1 = Me, R^2 = Ac).—Compound (7; R^1 = Me, R^2 = H) (3.43 g) was heated under reflux in acetic anhydride (20 cm³) and triethylamine (4 cm³) for 30 min. The solvent was removed *in vacuo*, and the oil obtained was dissolved in chloroform and basified with saturated aqueous sodium hydrogen carbonate. The organic layer was separated, dried ($MgSO_4$), and evaporated, to yield a solid which crystallised from ethanol as almost colourless *prisms* (3.9 g, 96%), m.p. 123—124°, *m/e* 264 (M^+), 222, 207 (base), and 144; $\nu_{max.}$ 1 685 and 1 600 cm⁻¹; δ 8.6 (1 H, d, *J* 1 Hz, pyridyl 2-H), 8.45 (1 H, d, *J* 7 Hz, pyridyl 6-H), 8.35 (1 H, s, indole 2-H), 7.48 (1 H, d, *J* 10 Hz, indole 7-H), 7.3—7.0

* We thank Mr. I. T. W. Matthews for this experiment.

(5 H, m, indole 4-, 5-, and 6- and pyridyl 4- and 5-H), 4.3 (1 H, q, *J* 7 Hz, C*H*·CH_3), 2.6 (3 H, s, Ac), and 1.7 (3 H, d, *J* 7 Hz, CH·C*H*$_3$) (Found: C, 77.1; H, 6.1; N, 10.7. $C_{17}H_{16}N_2O$ requires C, 77.3; H, 6.1; N, 10.6%).

3-[1-(*Indol-3-yl*)*ethyl*]*pyridine-4-carbonitrile* (10; R^1 = Me, R^2 = H).—1-Acetyl-3-[1-(3-pyridyl)ethyl]indole (7; R^1 = Me, R^2 = Ac) (2.59 g) was dissolved in dichloromethane (15 cm^3) and cooled to 0 °C. To this solution, *O*-mesitylsulphonylhydroxylamine (1 mol. equiv., 2.11 g) in cooled dichloromethane (20 cm^3) was added and the mixture was swirled. After *ca.* 15 min (with intermittent swirling) the solution was diluted with cooled, dry ether (250 cm^3), which caused an oil to separate. The ether was decanted, the oil was dissolved in ice-cooled water (25 cm^3), and acetic anhydride (20 cm^3) was added. The agitated mixture was then treated dropwise with aqueous 30% potassium hydroxide (15 cm^3) and maintained at room temperature for 1 h, before being poured into water (800 cm^3), basified with potassium carbonate, and extracted with chloroform. The organic phase was separated, dried ($MgSO_4$), and evaporated *in vacuo* to give an oil, *m/e* 321 (M^+), 279, 264, and 222 (base).

This product was treated with methyl iodide (20 cm^3) at reflux during 45 min. Removal of the excess of reagent left a yellow amorphous solid (4.2 g, 77.8%). This salt (4 g) in water (15 cm^3) was warmed to 20—22 °C and treated with ammonium chloride (2 mol. equiv., 0.93 g) and potassium cyanide (0.62 g) in water (6 cm^3). This mixture was stored for 1 h, during which time a pink precipitate was formed. The mixture was extracted with chloroform to yield, after removal of the solvent, an oil which was stirred in ethanol solution and irradiated with 'soft' u.v. light for 30 min. The solvent was removed under reduced pressure and the viscous oily residue was dissolved in chloroform and chromatographed over a short column of basic alumina (chloroform as eluant).

The first fractions were evaporated to give the *nitrile* (10; R^1 = Me, R^2 = H) as white prisms (2.0 g, 95%), m.p. 118—119° (from ethanol); *m/e* 247 (M^+) and 232 (base); $\nu_{max.}$ 3 140, 2 240, and 1 580 cm^{-1}; δ 8.66 (1 H, d, *J* 2 Hz, pyridine 2-H), 8.55 (1 H, d, *J* 6 Hz, pyridine 6-H), 8.25br (1 H, s, NH), 7.5—6.9 (6 H, m, indolyl 2-, 4-, 5-, 6-, and 7- and pyridine 5-H), 4.76 (1 H, q, *J* 9 Hz, CH·CH_3), and 1.79 (3 H, d, *J* 9 Hz, CH·C*H*$_3$) (Found: C, 77.8; H, 5.2; N, 16.9. $C_{16}H_{13}N_3$ requires C, 77.7; H, 5.3; N, 17.0%).

When, however, the reaction was repeated but the product was chromatographed on neutral alumina, the *N-acetyl derivative* (10; R^1 = Me, R^2 = Ac) was obtained as white prisms, m.p. 111—112° (from ethanol); *m/e* 289 (M^+) 247 and 232 (base); $\nu_{max.}$ 2 240, 1 705, and 1 600 cm^{-1}; δ ($CDCl_3$) 8.67 (1 H, d, *J* 2 Hz, pyridine 2-H), 8.6 (1 H, s, indolyl 2-H), 8.44 (1 H, d, *J* 10 Hz, pyridine 6-H), 7.46—7.1 (5 H, m, indolyl 4-, 5-, 6-, and 7- and pyridine 5-H), 4.68 (1 H, q, *J* 8 Hz, C*H*·CH_3), 2.68 (3 H, s, Ac), and 1.85 (3 H, d, *J* 8 Hz, CH·C*H*$_3$) (Found: C, 74.8; H, 5.4; N, 14.6. $C_{18}H_{15}N_3O$ requires C, 74.7; H, 5.2; N, 14.5%).

Ellipticine (2; R = Me).—The nitrile (10; R^1 = Me, R^2 = H) (200 mg) in dry ether (25 cm^3) was added slowly to a solution of methyl-lithium (4 mol. equiv.) in ether at −10 to −15 °C under nitrogen. Stirring was continued for 30 min at the same temperature, and then ice-cold water (10 cm^3) was introduced, followed by ammonium chloride (200 mg) in water (10 cm^3). The ethereal layer was removed, dried, and evaporated *in vacuo* to give the imine (12) as a gum, *m/e* 263 (M^+), 248 (base), and 231; $\nu_{max.}$ 3 360, 3 200, 1 640, and 1 595 cm^{-1}. The gum was dissolved in acetic acid (20%; 10 cm^3) and heated on a steam-bath for 10 min. A yellow fluorescence immediately developed. The solution was basified with potassium carbonate and extracted with chloroform. The organic layer was dried ($MgSO_4$), and evaporated *in vacuo* to give a yellow solid (188 mg, 92%), m.p. 311—312° (from chloroform) (lit.,[3g] 309—313°) (Found: C, 83.0; H, 5.6; N, 11.2. Calc. for $C_{17}H_{14}N_2$: C, 82.9; H, 5.7; N, 11.4%), identical (i.r. and u.v. spectra and chromatographic behaviour) with authentic ellipticine.[11]

11-*Demethylellipticine* (2; R = H).—The methylindole (7; R^1 = R^2 = H) was converted into its *N*-acetyl derivative (7; R^1 = H, R^2 = Ac) ($\nu_{max.}$ 1 720, 1 495, 1 460, and 1 050 cm^{-1}) which, without purification, was treated as described for (7; R^1 = Me, R^2 = Ac) to give, eventually, 3-[1-(1-*acetylindol-3-yl*)*ethyl*]*pyridine-4-carbonitrile* (10; R^1 = H, R^2 = Ac),* m.p. 157—158° (from ethanol); $\nu_{max.}$ 2 260 and 1 720 cm^{-1}; δ 8.84 (1 H, s, pyridine 2-H), 8.8—8.46 (2 H, m, pyridine 6- and indolyl 7-H), 7.64—7.28 (5 H, m, remaining aromatic protons), 4.32 (2 H, s, CH_2), and 2.64 (3 H, s, Ac) (Found: C, 74.2; H, 4.7; N, 15.2. $C_{17}H_{13}N_3O$ requires C, 14.1; H, 4.8; N, 15.3%). This compound was eluted in chloroform through a short column packed with basic (Merck) alumina and the crude product (10; R^1 = R^2 = H) was dissolved in tetrahydrofuran and treated with methyl-lithium as described for (10; R^1 = Me, R^2 = H). The intermediate imine was hydrolysed with 2M-hydrochloric acid to afford 11-demethylellipticine as pale yellow crystals [overall yield from (7; R^1 = R^2 = H), 28%], m.p. 275—277° (lit.,[12] 276°), *m/e* 232 (M^+) and 208 (base); $\lambda_{max.}$ (0.1M-HCl in 85% EtOH) 238 (ε 27 000), 248sh (25 000), 270sh (20 000), 307 (73 000), and 350 nm (7 000); $\nu_{max.}$ 1 605 and 1 250 cm^{-1} (Found: C, 82.8; H, 5.1; N, 12.0. Calc. for $C_{17}H_{12}N_2$: C, 82.7; H, 5.2; N, 12.1%).

5,6-*Methylenedioxy*-3-[1-(3-*pyridyl*)*ethyl*]*indole* (12; R = Ac).—(*a*) 5,6-Methylenedioxyindole [10] was combined with the chloropyridine (8; X = Cl) as described for the preparation of (7; R^1 = Me, R^2 = H). However, since we had a limited quantity of the indole, a mixture of ethylmagnesium bromide, the indole, and the chloropyridine was used, in the molar ratios 1 : 1 : 1. The product was obtained as white *prisms* (12%), m.p. 182—183° (from ethanol); *m/e* 266 (M^+) and 251 (base); $\nu_{max.}$ 3 100, 1 590, 1 580, 1 300, and 1 030 cm^{-1}; δ [$CDCl_3$–6% $(CD_3)_2SO$] 10.17br (1 H, s, NH), 8.52 (1 H, s, pyridyl 2-H), 8.37 (1 H, d, *J* 6 Hz, pyridyl 6-H), 7.54 (1 H, m, pyridyl 4-H), 7.15 (1 H, m, pyridyl 5-H), 6.94 (1 H, s, indole 2-H), 6.82 (1 H, s, indole 7-H), 6.6 (1 H, s, indole 4-H), 5.81 (2 H, s, O·CH_2·O), 4.25 (1 H, q, *J* 9 Hz, C*H*·CH_3), and 1.63 (3 H, d, *J* 9 Hz, CH·C*H*$_3$) (Found: C, 72.1; H, 5.4; N, 10.7. $C_{16}H_{14}N_2O_2$ requires C, 72.2; H, 5.3; N, 10.5%).

(*b*) The reaction was repeated, but in dry tetrahydrofuran, and the mixture was heated under reflux for 1 h. The yield of product was only 6%.

(*c*) The experiment was repeated with methyl-lithium instead of ethylmagnesium bromide. The yield of final product was 3%.

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1-*Acetyl*-5,6-*methylenedioxy*-3-[1-(3-*pyridyl*)*ethyl*]*indole* (12; R = Ac).—The indole (12; R = H) was converted into the acetyl derivative as described for the unsubstituted compounds, to give white *crystals* (93%), m.p. 160—161° (from ethanol); *m/e* 308 (M^+), 266, and 251 (base); $\nu_{max.}$ 1 690 and 1 600 cm^{-1}; δ 8.6 (1 H, s, pyridyl 2-H), 8.38 (1 H, d, *J* 6 Hz, pyridyl 6-H), 7.92 (1 H, s, indole 7-H), 7.5 (1 H, m, pyridyl 4-H), 7.14 (1 H, m, pyridyl 5-H), 7.08 (1 H, s, indole 2-H), 6.5 (1 H, s, indole 4-H), 5.9 (2 H, s, O·CH_2·O), 4.1 (1 H, q, *J* 9 Hz, C*H*·CH_3), 2.6 (3 H, s, Ac), and 1.65 (3 H, d, *J* 9 Hz, CH·C*H*$_3$) (Found: C, 70.1; H, 5.3; N, 9.0. $C_{18}H_{16}N_2O_3$ requires C, 70.1; H, 5.2; N, 9.1%).

3-[1-(1-*Acetyl*-5,6-*methylenedioxyindol*-3-*yl*)*ethyl*]*pyridine*-4-*carbonitrile* (13).—The indole (12; R = Ac) was converted, by a series of steps similar to those already described, into the title *compound*, which was obtained as a white crystalline solid, after chromatography on neutral alumina and elution with chloroform [yield from (12; R = H), 79%]; m.p. 196—197°; *m/e* 333 (M^+), 291, 276 (base), and 251; $\nu_{max.}$ 2 200, 1 690, and 1 590 cm^{-1}; δ 8.53 (1 H, d, *J* 6 Hz, pyridine 6-H), 8.5 (1 H, s, pyridine 2-H), 7.9 (1 H, s, indolyl 7-H), 7.23 (1 H, d, *J* 6 Hz, pyridine 5-H), 7.18 (1 H, s, indolyl 4-H), 6.43 (1 H, s, indolyl 2-H), 5.9br (2 H, s, O·CH_2·O), 4.55 (1 H, q, *J* 8 Hz, C*H*·CH_3), 2.63 (3 H, s, Ac), and 1.78 (3 H, d, *J* 7 Hz, CH·C*H*$_3$) (Found: C, 68.7; H, 4.6; N, 12.5. $C_{19}H_{15}N_3O_3$ requires C, 68.5; H, 4.5; N, 12.6%).

8,9-*Methylenedioxyellipticine* (14).—The nitrile (13), after elution in chloroform through a basic alumina column, was treated with an excess of methyl-lithium, and the product was worked up in the usual manner to give the corresponding imine. This was transformed into the title compound by heating in 2M-hydrochloric acid for 30 min, basifying with sodium hydrogen carbonate and extracting with chloroform. Evaporation of the organic phase under reduced pressure furnished the yellow 8,9-methylenedioxyellipticine [65% from (12; R = H)], m.p. 330—333° (decomp.) (from ethanol) (lit.,[3i] 333°); *m/e* 290 (M^+, base), 275, 261, 251, and 231; $\nu_{max.}$ 3 300, 1 620, 1 580, and 1 020 cm^{-1}; $\lambda_{max.}$ 213 (ε 40 000), 229 (38 200), 249 (28 500), 273sh (45 400), 283 (58 000), 316 (72 500), and 246 nm (15 500); δ [$(CD_3)_2SO$] 11.15 (1 H, s, NH), 9.72br (1 H, s, 1-H), 8.48 (1 H, dd, *J* 8 and 2 Hz, 3-H), 7.97 (2 H, m, 4- and 10-H), 7.2 (1 H, s, 7-H), 6.2 (2 H, s, O·C*H*$_2$·O), 3.22 (3 H, s, CH_3), and 2.79 (3 H, s, CH_3) (Found: C, 74.4; H, 5.0; N, 9.6. Calc. for $C_{18}H_{14}N_2O_2$: C, 74.5; H, 4.9; N, 9.7%).

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